Clinical Medicine and Integrative Therapies

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Review

Novel Therapeutics in the Management of Autoimmune Disorders: A Narrative Review

Obiora Emmanuel Abonyi[1], Virginus Agozie Umeh[2,*], Nancy Oluomachi Uchenna[2]

[1]Department of Biochemistry, College of Medicimne, Enugu State University of Science and Technology, Enugu, Nigeria

[2]Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike, Abia State Nigeria

[*]Corresponding author: Virginus Agozie Umeh, umeh.virginus@mouau.edu.ng

Abstract

Autoimmune and chronic inflammatory diseases are common challenges to global health. Previous studies have emphasized that therapy with traditional immunomodulators relied on strategies of either immunosuppression or stimulation. However, new knowledge about immunity has led to treatments that are more effective at resolving the disease's pathways, with fewer serious side effects. As no immune disorder is static, this review focuses on current therapeutic strategies for immune disorders: biologics, small-molecule inhibition, cell therapy, and gene editing. Anti-Tumour necrosis factor (TNF) and Interleukin (IL)-17 inhibitors, for example, have been helpful in diseases such as rheumatoid arthritis (RA) and psoriasis, cytokines being biologics. Small-molecule inhibitors, such as Janus kinase (JAK) inhibitors, are oral therapies used to manage conditions such as ulcerative colitis. Among the cellular therapies, the principles of hematopoietic stem cell transplantation (HSCT) and Chimeric Antigen Receptor T-cell (CAR T cell) therapy have the potential to reprogram the immune system for long-term control. Furthermore, gene editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) and ribonucleic acid (RNA) therapeutics are opening up the options for precise medicine. Biomarker-guided and pharmacogenomic treatment plans make the patient experience as effective as possible while minimising side effects. Some of the challenges identified include safety, cost, and accessibility thresholds for these therapies, as presented in the challenges and future directions section.

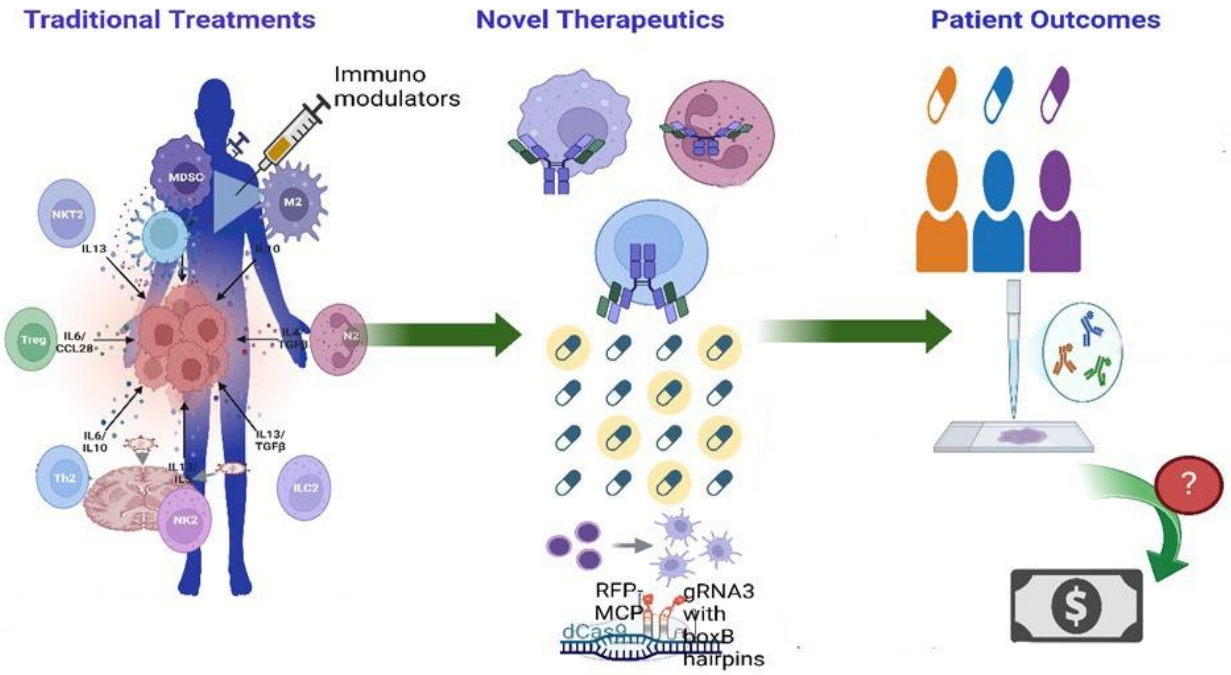
Keywords

Autoimmune diseases, Biologicals, Cell therapies, Cell and gene therapy, JAK inhibitors, Individualized treatments

Article History

Received: 23 November 2025 Revised: 15 January 2026

Accepted: 21 January 2026 Available Online: 06 February 2026



Graphical abstract illustrating the different management options for different immune disorders, from traditional treatments to exact modern methods. It shows how the immunomodulatory treatment methods, which in general affect a wide range of immune cells and cytokine networks are superseded by more specific treatment methods. The main panel puts the emphasis on precision modalities as biologics, cell-based therapies, and gene-editing technologies aimed at the selective regulation of the immune pathways. Such innovations are meant to enhance patient outcome, e.g. by using personalized treatments, biomarker-based monitoring, and a more cost-effective and outcome-based care.

1. Introduction

Immune disorders, including autoimmune diseases and chronic inflammatory conditions, are diseases of the immune system in which impaired immune responses lead to a failure to distinguish between self-tissues and foreign antigens [1]. These diseases are common and estimated to affect millions of individuals worldwide. Examples include rheumatoid arthritis (RA), multiple sclerosis, inflammatory bowel disease (IBD), and systemic lupus erythematosus [2,3]. All of these disorders involve intricate immunopathological processes in which immune cells, cytokines, and signal transduction pathways act in concert to cause tissue injury and progressive disease [4,5]. Historically, the treatment of immune disorders has emphasized broad suppression of the immune system to reduce inflammation and slow disease progression [6]. Corticosteroids, methotrexate, and other conventional immunosuppressive agents have served as mainstay therapies, reducing disease manifestations through generalized inhibition of immune responses [7]. Despite evidence supporting their clinical efficacy, the nonselective nature of these drugs is associated with significant adverse effects, including an increased risk of infections, reduced bone density, and hepatic or renal toxicity [8]. Consequently, there has been a growing need for therapeutic interventions that selectively target specific immune pathways while preserving essential immune functions.

Over the last several decades there have been significant breakthrough in immunology and molecular biology that have dramatically altered the therapeutic approach to immune disorders. They summarize advances in knowledge of the immunopathogenesis of these diseases and new drugs targeting cells and cytokines and immune processes fundamental to these illnesses. Anti-Tumour necrosis factor (TNF) and Interleukin (IL) monoclonal antibodies, small molecule inhibitors such as JAK inhibitors, and novel cell therapies have shown that these drugs are useful for controlling symptoms and achieving remission in many patients with autoimmune diseases [9-11]. Also gene-editing technologies and RNA-based therapies are being searched as potentially lucrative interventions which could alter the disease trajectory at genetic, cellular or molecular level, which may possibly offer durable or even irreversible benefits [12-14].

This paper aimed to review and briefly describe these new immuno modulating agents; their mode of action, evidence from randomized controlled trials (RCTs) in the management of immune disorders, and side effects. Equally, it contemplates how the concept of individualized medicine could enhance the administration of strategies. Some of the development in biomarkers, pharmacogenomics is opening up a new era of personalized immune treatments thereby enhancing chances of a proper response with negligible side effects. The field of immune therapeutics is slowly evolving into the future not only where the therapeutics are more efficient, but also more specific according to the manifestations

of the immune system [15]. It should noted that these solutions are still far from perfect with regard to availability, affordability, and sustainability. It is the purpose of this article to consider these developments and to elucidate the opportunities and pitfalls of emerging therapeutics for immunological diseases.

1.1 Rationale

Globally immune disorders have emerged as a significant issue of social health due to their resulting high morbidity along with reduced quality of life and higher health costs. The main ways of treating the symptoms are broad immune inhibition drugs such as corticosteroids in combination with methotrexate but carry several side effects combined with their temporary success. The more selective, potent and more tolerable approaches to treatment have become a mandatory requirement in instances of refractory or relapsing disease. The studies of the past several decades have spurred a paradigm shift in immunotherapy, which has been possible due to the development of molecular immunology, bioengineering, and pharmacogenomics. Medical innovation in the treatment of diseases is exhibited by new biologics and pharmacologic therapies targeting particular cytokines tumor necrosis factor-a, IL-6 and IL-17 and small molecule drugs JAK and Sphingosine-1-phosphate (S1P) modulators and cellular therapy CAR-T cells and regulatory T-cells to provide personalized immune control with fewer adverse systemic effects. Gene editing methods such as CRISPR-Cas9 and RNA-based therapies offer fundamental changes to therapeutic frontiers since these methods offer a customized approach to disease modification.

The dynamic nature of the therapeutic environment requires the professionals in the healthcare field to compile the latest facts to aid in making medical decisions and identify informational gaps to stimulate innovations. It is reasonable to review the recent immune therapeutic advances since it enables us to put together the new therapeutic approaches and the mechanisms behind the therapeutic success and possible challenges. This review provides the data on new intervention safety and efficacy and discusses some of the most important issues like access to care of patients, integration of biomarker-based with the pharmacogenomic-based personalized therapeutic approaches.

This paper examines both proven and research-based therapies in order to provide awareness on the value of ongoing research through the application of translation and to forecast future trends that influence the management of immune disorders. Precision medicine that will be dual-inclusion coupled with next-generation therapeutic platforms will simplify a new future that will entail safe and effective approaches to immune modulations of heterogeneous and multifactorial immunological illnesses. The review is needed in scholarly terms at this moment because it presents essential research to the healthcare professionals and scientists, policy makers that wish to improve the outcomes of immune disorder treatment.

2. Methodology

Objectives: This narrative review aims to explore recent advancements in novel therapeutics for immune disorders, with emphasis on biologics, small-molecule inhibitors, gene and cell-based therapies, and precision medicine approaches. It seeks to summarize emerging evidence, therapeutic mechanisms, and translational implications for the management of autoimmune and chronic inflammatory diseases.

2.1 Eligibility Criteria

The review included literature based on the following criteria:

Population: Individuals with autoimmune or chronic inflammatory immune disorders (e.g., RA, lupus, IBD, MS).

Intervention: Novel therapies such as biologics, JAK inhibitors, CAR-T cells, HSCT, CRISPR-based gene editing, RNA-based treatments, and pharmacogenomics-guided strategies.

Outcomes: Evidence of therapeutic efficacy, safety, mechanisms of action, and precision applications.

Study Types: RCTs, observational studies, preclinical studies, systematic reviews, expert guidelines, and narrative reviews.

Language: English

Timeframe: January 2015 - April 2025

Excluded studies were:

Irrelevant to immune disorders (e.g., cancer-only studies without autoimmune overlap).

Opinion pieces without original data.

Studies focusing exclusively on conventional therapies.

Non-English articles or those without accessible full texts.

2.2 Information Sources and Search Strategy

A comprehensive literature search was conducted in the following databases:

PubMed/MEDLINE, Embase, Scopus, Web of Science, Google Scholar

Search terms included combinations of:

"immune disorders", "autoimmune diseases", "biologics", "JAK inhibitors", "CAR-T therapy", "gene editing", "CRISPR", "RNA therapy", "immunotherapy", "precision medicine" and "novel treatments".

2.3 Selection and Data Charting Process

Studies were screened by title and abstract, followed by full-text review. Selection was independently verified. Extracted data included author/year, disease focus, intervention type, mechanism of action, therapeutic outcomes, and safety profiles. No formal quality appraisal was performed, given the narrative nature of the review.

Synthesis of Results

A thematic analysis was employed. Findings were categorized under:

(1) Biologics and cytokine targeting

(2) Small molecule inhibitors

(3) Cell-based therapies

(4) Gene editing and RNA therapeutics

(5) Precision and individualized medicine

The synthesis aimed to highlight therapeutic innovations, clinical applicability, limitations, and prospects.

3. Practical Innovations Related to Therapeutic Model

Practical innovations are associated with therapeutic models that aim to integrate enhanced technologies, individualized therapies, and novel drug delivery systems to improve patient outcomes. Such inventions include targeted biologics and small-molecule inhibitors, cell-based treatments, gene editing, and RNA-based treatments, as well as precision medicine in the field of autoimmune diseases to optimize diagnostics and treatment, ultimately leading to greater precision and efficiency in healthcare. An overview of these innovations, in contrast to conventional methods of immune disorder management, is presented in Figure 1, while Table 1 classifies therapies according to clinical maturity.

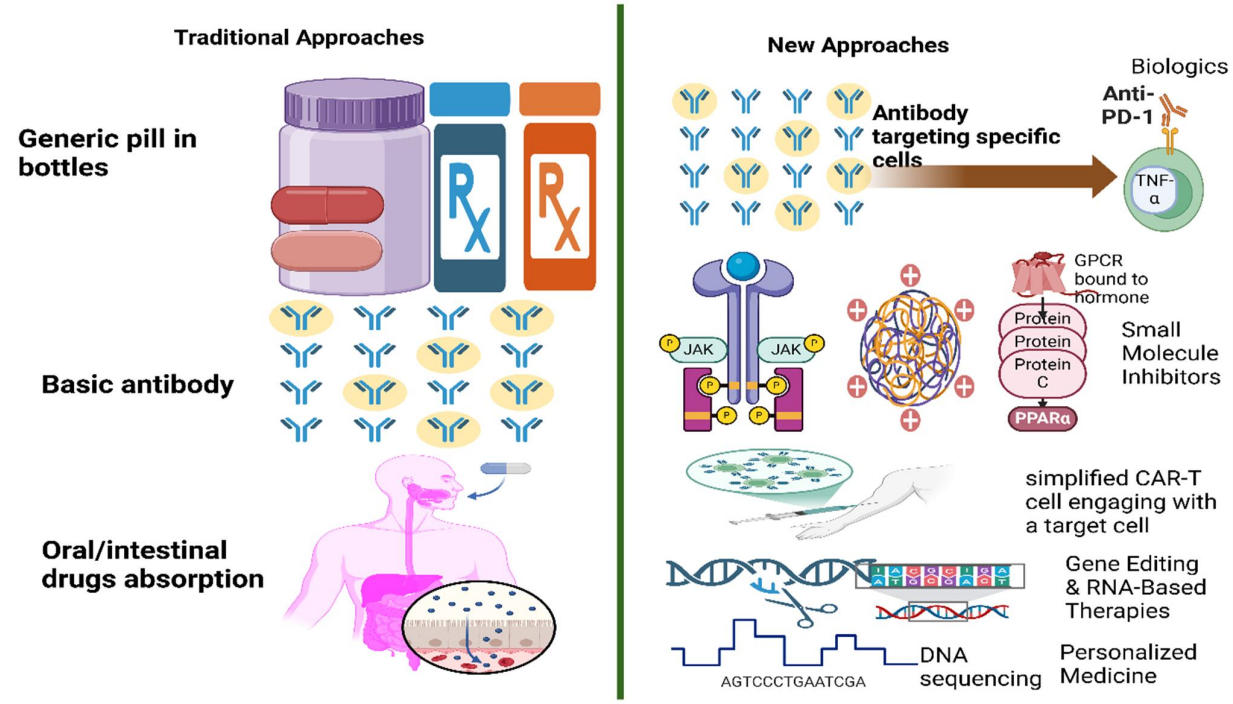


Figure 1. Different therapeutic approaches to management of immumological disorders old vs new.

Figure 1 showed different therapeutic approaches to management of immunological disorders old vs new viz: Biologics (Anti-IL-6 Therapy, Anti TNF Therapy, Anti-IL-17 and Anti-IL-23 Therapy, B-Cell Targeting Agents, Checkpoint

Inhibitors, Anti-IgE Therapy), Small Molecule Inhibitors (JAK Ihibitors, S1P Receptor Modulators. Phosphodiesterase-4 (PDE4)Inhibitors) Cell-Based Therapies (HSCT, Chimenic Antigen Receptor T-Cell Therapy, Regulatory T-Cell (Treg)Therapy), Gene Editing and RNA-Based Therapies (CRISPR-Cas9 for Genetic Correction, RNA Interference (RNAi) and Antisense Oligonucleotides). Personalized and Precision Medicine in Immune Disorders (Biomarker-Guided Therapy, Phammacogenomics)

Table 1. Stratification of therapeutic innovations by clinical maturity in autoimmune diseases.

Therapeutic Category	Specific Therapies / Examples	Clinical Maturity	Current Status and Notes
Biologics	Anti-TNF agents (infliximab, adalimumab, etanercept)	Approved / Established	Standard of care for RA, IBD, psoriasis; extensive long-term evidence
Biologics	Anti-IL-6 agents (tocilizumab, sarilumab)	Approved / Established	Approved for RA and JIA; effective in cytokine-driven inflammation
Biologics	Anti-IL-17 agents (secukinumab)	Approved / Established	Approved for psoriasis, psoriatic arthritis, and ankylosing spondylitis
Biologics	Anti-IL-23 / IL-12/23 agents (ustekinumab)	Approved / Established	Approved for psoriasis, psoriatic arthritis, Crohn's disease
Biologics	B-cell targeting agents (rituximab, belimumab)	Approved / Established	Belimumab is FDA-approved for SLE; rituximab is widely used off-label
Biologics	Anti-IgE therapy (Omalizumab)	Approved / Established	Approved for severe allergic asthma and chronic spontaneous urticarial
Biologics	Checkpoint inhibitors (PD-1, PD-L1, CTLA-4 modulation)	Early–Late Clinical Trials	Approved in oncology; autoimmune applications under investigation
Small-Molecule Inhibitors	JAK inhibitors (tofacitinib, baricitinib, upadacitinib)	Approved / Established	Approved for RA, PsA, UC; oral alternatives to biologics
Small-Molecule Inhibitors	S1P receptor modulators (fingolimod, siponimod)	Approved / Established	Approved for multiple sclerosis; regulates lymphocyte trafficking
Small-Molecule Inhibitors	PDE4 inhibitors (apremilast)	Approved / Established	Approved for psoriasis and psoriatic arthritis
Cell-Based Therapies	HSCT	Late-Stage / Selective Use	Used in severe refractory autoimmune diseases; high efficacy with procedural risks.
Cell-Based Therapies	CAR T-cell therapy	Early Clinical Trials	Approved for malignancies; limited autoimmune proof-of-concept studies
Cell-Based Therapies	Regulatory T-cell (Treg) therapy	Early Clinical / Translational	Promising early trials; scalability and durability under evaluation
Gene Editing & RNA-Based	CRISPR-Cas9 gene editing	Preclinical–Early Clinical	Experimental; safety and off-target effects under study
Gene Editing & RNA-Based	RNAi	Early Clinical / Translational	Targets inflammatory mediators; delivery challenges persist
Gene Editing & RNA-Based	Antisense oligonucleotides (ASOs)	Early–Late Clinical Trials	Advancing in IBD and lupus; high molecular specificity
Precision Medicine	Biomarker-guided therapy	Clinically Implemented (Adjunctive)	Used to optimize biologic selection and treatment response
Precision Medicine	Pharmacogenomics	Early Clinical Adoption	Emerging role in guiding immunomodulatory therapy

Table 1 summarizes the therapeutic innovations discussed in this review, stratified by clinical maturity, from approved and established therapies to late-stage and early/preclinical approaches. It highlights the current translational status of biologics, small-molecule inhibitors, cell-based therapies, gene editing, RNA-based strategies, and precision medicine in autoimmune diseases. This stratification provides a clear overview of which innovations are ready for routine clinical use versus those that remain investigational or emerging.

3.1 Biologics

The healthcare revolution has introduced breakthrough biological agents that improve the treatment of immune diseases. The biologics used in modern therapeutic compounds are derived from living cells to produce protein-based compounds. Such medical products aim to tailor specific areas of the immune system, enabling the medical practitioner to fine-tune the management of biological processes associated with the disease. The selectivity of these medicines is much more

advantageous compared to the traditional immunosuppressive drugs since they are general and non-selective in their actions to initiate systemic a [16] diverse effects and general immune-suppression, respectively. The biologic treatments are more effective in the therapy of patients with inflammatory or autoimmune diseases as the targeted intervention of the specific immune activation molecules is performed and the adverse effects are reduced to provide the enhanced clinical outcome in patients [16]. A discussion of the effects of biologic drugs on medical diseases and subsequent complications of using these drugs in clinical practice elaborates on both the mechanisms of operation of these drugs and their treatment effects on treating autoimmune and inflammatory diseases. Table 2 provides a recap of the key therapeutic classes of biologic, target molecule, and the mode of action, and key clinical indications.

Table 2. Summary of major biologic therapeutic classes in Immune disorders.

Therapeutic Class	Target Molecule	Mechanism of Action	Key Clinical Indications	References
Anti-TNF Therapy	TNF-α	Neutralizes TNF-α to inhibit downstream inflammatory cascade	RA, Crohn's disease, ulcerative colitis, psoriasis	[17-19]
Anti-IL-6 Therapy	IL-6 receptor	Blocks IL-6 receptor, reducing cytokine-mediated inflammation	RA, juvenile idiopathic arthritis	[19-23]
Anti-IL-17 Therapy	IL-17A	Binds IL-17A to suppress Th17-mediated inflammation	Psoriasis, psoriatic arthritis, ankylosing spondylitis	[24-26]
Anti-IL-23 Therapy	IL-12/23 p40 subunit	Inhibits IL-12/23 signaling to prevent Th17 differentiation	Psoriasis, Crohn's disease, psoriatic arthritis	[27-29]
B-Cell Targeting Agents	CD20 (Rituximab), BAFF (Belimumab)	Depletes B cells or inhibits survival factor to suppress autoantibody production	Systemic lupus erythematosus, RA, multiple sclerosis	[30-32]
Checkpoint Inhibitors	PD-1, PD-L1, CTLA-4	Modulates T-cell activation by blocking inhibitory checkpoints	Under investigation in autoimmune diseases, approved in cancer	[33-36]
Anti-IgE Therapy	IgE	Binds free IgE, preventing mast cell and basophil activation	Severe allergic asthma, chronic spontaneous urticaria	[37-42]

Table 2 summarizing the major therapeutic classes of biologics, their target molecules, mechanisms of action, and key clinical indications.

3.1.1 Anti-TNF Therapy

The oldest available biologic agents class which received broad medical acknowledgment are anti-tumor necrosis factor inhibitors. The cytokine TNF-α functions as an intense inflammatory factor that both drives immune system operations and supports inflammatory responses. According to recent research, the excessive production of TNF-α develops all RA, along with psoriasis, ulcerative colitis, and Crohn's disease [17]. The drug industry has developed the prominent pharmaceutical compounds infliximab, adalimumab, and etanercept for manufacturing purposes. Biologic agents inhibit TNF-α activity by binding TNF-α, halting, receptor interaction, and blocking circulating TNF-α activity. Data show that blocking TNF-α stops inflammatory cascades, slows disease progression, and diminishes tissue destruction [18]. Scientific investigations into TNF-α blocking drugs transformed chronic autoimmune therapy by achieving effective improvements in clinical features and patient function and enhanced quality of life. These symptoms of painful destructive arthritis previously experienced by patients have resulted in prolonged disease-free periods accompanied by reduced flare-ups. A particular group of patients resists all treatment options because primary non-responders represent thirty percent of all cases but patients become resistant to medications when disease characteristics change and anti-drug antibodies develop [19]. The existing healthcare conditions lack satisfactory outcomes so healthcare must establish patient-tailored treatment methods and new biologic pharmaceuticals.

3.1.2 Anti-IL-6 Therapy

Interleukin(IL)-6 performs as a principal pro-inflammatory cytokine that rules various types of immune activation in patients who have autoimmune diseases including RA and juvenile idiopathic arthritis (JIA). IL-6 plays a vital role in immunological management since it activates T cells and drives B-cell proliferation as well as acute-phase protein generation. The medications toclizumab and sarilumab work as monoclonal antibodies to limit IL-6 receptor activity thus reducing IL-6 levels to decrease inflammation [20]. Research shows that these treatments effectively treat patients who fail to achieve sufficient outcomes with TNF inhibitor therapies establishing a new procedure for disease progress control. Scientific research shows that blocking IL-6 activity creates two beneficial outcomes which stop joint damage and minimize systemic inflammation through reductions of C-reactive protein levels [21,22]. These treatments demonstrate additional benefits for healthcare because research shows they help manage cytokine release syndromes and improve the condition of severe COVID-19 patients whose IL-6 levels are elevated [23].

3.1.3 Anti-IL-17 and Anti-IL-23 Therapy

Autoimmune processes that activate IL-17 and IL-23 maintain the progression of psoriasis as well as psoriatic arthritis and IBD [24]. The activity of Th17 cells emerges from cytokines serving to create persistent skin tissue inflammation and joint damage and activate mucosal tissue inflammation. Scientific evidence shows anti-IL-17A agent secukinumab and anti-IL-12/23 agent ustekinumab achieve clinical success by blocking these precise pathways [25,26]. The IL-17A pathway ends with secukinumab treatment so it helps manage inflammatory conditions simultaneously with promoting skin lesion healing while ustekinumab interrupts p40 to stop IL-12 and IL-23 binding for blocking Th17 cell activation along with prolongation [27,28]. The therapeutic approaches give rheumatoid disease patients maximizing benefits when standard disease modifying anti-rheumatic drugs (DMARDs) do not generate sufficient treatment responses. Data show that this treatment system controls symptoms while shrinking tissue damages which makes it an effective approach to handle complex autoimmune illnesses [29].

3.1.4 B-Cell Targeting Agents

A set of autoimmune diseases relies on the B cell functions to establish autoantibodies and present antigens and release cytokines which together support the pathogenic progression. Studies prove that abnormal B-cell functioning in systemic lupus erythematosus (SLE) multiple sclerosis (MS) and RA results in raised tissue inflammation that intensifies disease symptoms [30] Rituximab serves as a chimeric monoclonal antibody that reaches CD20 on B cells to trigger B cell depletion while demonstrating effective therapeutic outcomes for B-cell operative diseases [31]. The therapy demonstrates its greatest worth during patient treatment when RA combines with positive serology and persistent systemic lupus erythematosus. The B-cell modulating therapy belimumab attacks B-cell activating factor (BAFF) to eliminate its vital role in B-cell development and survival. The Food and Drug Administration marked this biologic as their initial SLE treatment by approving it to improve disease status yet reduce flare intensity [32]. These agents create proven therapeutic paths to control damaging harm that B-cells cause during autoimmune damage.

3.1.5 Checkpoint Inhibitors

Scientific teams first applied checkpoint inhibitors to cancer therapy before identifying these agents as potential regulators of autoimmune diseases. The checkpoint regulator molecules PD-1/PD-L1 (Programmed Death-1/Programmed Death-Ligand 1) and CTLA-4 (Cytotoxic T-Lymphocyte–Associated Antigen 4) serve natural brakes on T-cell activation so blocking these pathways prevents T-cell activation [33] Autoimmune damage occurs from improper T-cell activation which produces prolonged inflammation and tissue injury. The use of checkpoint modifier interventions may allow scientists to restore immune tolerance while simultaneously blocking T-cell auto-reactivity. The research about checkpoint blockade for diseases such as type 1 diabetes, autoimmune encephalitis and refractory RA carries preliminary findings from preclinical and initial clinical trials [34-36]. Medical use of checkpoint inhibitors in non-malignant diseases needs careful consideration by health professionals because these treatments can cause serious adverse immune side effects. Future research demands the discovery of approaches that balance the immune system activation with immune system suppression.

3.1.6 Anti-IgE Therapy

Immunoglobulin-E (IgE) functions as the principal mediator of allergic responses so physicians employ it as their therapeutic target for treating allergic asthma and chronic urticaria. Omalizumab therapy provides benefit for risk-resistant severe asthma patients and chronic hives patients whose symptoms persist after antihistamine and corticosteroid treatments because Omalizumab functions as a recombinant humanized monoclonal antibody preventing IgE from connecting to mast cells and basophils to lower hypersensitivity reactions [31,37]. Anti-IgE therapy reaches its therapeutic effects by fixing the allergic cascade at the first steps while improving lung function and reducing asthma flare-ups leading to enhanced patient health. Healthcare staff need to examine how anti-IgE therapy fits into food allergy management together with atopic dermatitis and other IgE-mediated issues before establishing its central position in picking treatments for certain allergic diseases [38]. Biologic medications have become essential for treating conditions that present with immune-medicated pathophysiology. The molecular mechanism of biologic drugs regulates immune responses in patients while maintaining overall immune functioning unlike regular immunosuppressant medications. These drugs effectively control diseases while minimizing their systemic side effects so they transform various persistent autoimmune and inflammatory conditions [39] though such drugs still have disadvantages. High expense of biologic drugs prevents their medical use across patient populations residing in low- and middle-income countries. These treatments generate concerns for healthcare professionals because they produce long-lasting impacts on immune responses and both infections patterns alongside treatment benefit sustainability. Patients find biologic drugs difficult to handle because they require administration by injection methods thus leading to lower adherence rates [40,41]. The continuous research on biologic therapies targets two areas: the development of better biomarkers for patient selection and improved treatment strategies including dosage methods and multiple therapy evaluation [42]. Researchers in pharmacological innovation will enhance treatment accuracy through their work developing biosimilar medications and oral versions of biologic drugs.

3.2 Small Molecule Inhibitors

Small molecule inhibitors offer increased therapeutic potential in immunomodulatory therapy since it is simply taken orally by patients who prefer oral medications as opposed to injected biologics or cannot be treated with biologics [43]. These agents constitute compounds or molecules of small molecular weight structures that pass cellular barriers to influence signaling cascades that regulate immune response activities. These medications allow them to be orally ingested and quickly excreted out of the body, and they reach different tissues effectively thus making them effective to control chronic inflammatory diseases in the body on a long-term basis [44,45]. Table 3 illustrates these features.

Table 3. Immunomodulatory therapies: Mechanisms and clinical use.

Class of Inhibitor	Target Molecule	Mechanism of Action	Key Clinical Indications	Cost Effectiveness	References
JAK Inhibitors	JAK enzymes (JAK1, JAK2, JAK3, Tyk2)	Inhibit the JAK-STAT signaling pathway, reducing cytokine signaling involved in inflammation	RA, psoriatic arthritis, ulcerative colitis	Moderate to High: Oral formulations are cost-effective compared to biologics; generics are emerging	[46-48]
S1P Receptor Modulators	S1P receptor	Modulate immune cell trafficking by inhibiting lymphocyte egress from lymph nodes	Multiple sclerosis, autoimmune diseases with lymphocyte infiltration	High: Expensive; often requires prior authorization and insurance due to >\$80,000/year cost	[49]
PDE4 Inhibitors	PDE4	Increase intracellular cAMP, reducing pro-inflammatory cytokine production	Psoriasis, psoriatic arthritis, chronic inflammatory conditions	Moderate: Oral administration reduces costs; fewer monitoring requirements than biologics	[51-57]

Table 3 summarizes the major classes of small-molecule immunomodulatory therapies, highlighting their molecular targets, mechanisms of action, and key clinical indications in autoimmune and inflammatory diseases. It also compares their relative cost-effectiveness, emphasizing the advantages of oral administration while noting economic and access considerations across different inhibitor classes.

3.2.1 JAK Inhibitors

JAK-STAT signaling pathway using the JAK proteins is executed in the cells receiving tofacitinib and baricitinib and upadacitinib [46,47]. The body transmits information via this signaling network to the pro-inflammatory genes that are present in the nucleus after the cytokine receptors signal. This category of drugs inhibits the JAK enzymes to prevent the activation of multiple cytokines in autoimmune diseases. These management therapies are suitable in patients with RA and psoriatic arthritis and ulcerative colitis and have oral convenience and safety properties over biologics [48].

3.2.2 S1P Receptor Modulators

Fingolimod and siponimod serve as agents that bind to the S1P receptor to regulate lymphocyte movement between tissues. Lymphocytes become trapped inside lymph nodes through treatment drugs blocking their ability to exit into peripheral tissues that reduce immune damage in multiple sclerosis patients. These medications brought a new standard for MS relapse management as well as neuroinflammatory regulation in multiple sclerosis patients [49].

3.2.3 PDE-4 Inhibitors

The Phosphodiesterase-4 (PDE-4) inhibitors achieve their immunomodulatory action by selectively blocking enzyme PDE-4, which is involved in the degradation of intracellular cyclic adenosine monophosphate (cAMP) of immune and inflammatory cells [50]. The agents, including apremilast, prevent the breakdown of cAMP and consequently raise intracellular cAMP levels that in turn stimulates protein kinase A and consequently suppresses the signaling pathways that promote pro-inflammatory responses [51]. This causes the decrease of production of major inflammatory mediators, which are tumor necrosis factor-a TNF-a, IL-17, IL-23, and interferon-g, and the increase of anti-inflammatory cytokine production, such as IL-10. By such mechanisms, the inhibition of PDE-4 has a wide-ranging anti-inflammatory and immunoregulatory effect with no generalized immunosuppression [52]. Several studies have shown that Pemalist can be used to manage psoriasis and psoriatic arthritis, especially in patients with a high need of an effective oral treatment and more tolerable safety profile than the traditional systemic immunosuppressants or biologic treatment [53, 54]. It's orally, the relatively long-lasting laboratory monitoring-free, and comparably mild adverse-effect profile, (the most frequent adverse-effects being gastrointestinal symptoms and headache) make it an appealing choice in chronic inflammatory patients. Notably, there has been a rise in clinical evidence to reinforce the effectiveness of apremilast in the management of refractory oral aphthosis, particularly in the presence of Behcet's disease, a multisystem inflammatory disease that is

typified by recurrent and painful oral ulcers [55]. Controlled trials have also proven that apremilast shows significant effect in reducing the frequency and intensity of oral ulcers, as well as pain, in patients with Behcet disease unresponsive or intolerant of traditional treatments [56]. These are the benefits which are seen at the beginning of treatment and is maintained with further therapy. Consequently, apremilast was approved by the regulatory authorities to be used in the context of oral ulcers of Behcet disease in a number of different states, which has demonstrated its clinical applicability in non-dermatologic contexts. Altogether, PDE4 inhibitors including apremilast can broaden the treatment options of a variety of chronic immune-mediated and inflammatory conditions, providing a therapeutic alternative with its own activity, safety, and tolerability [57].

3.3 Cell-Based Therapies

Ways of treatment, based on the use of the cell, and more specifically, immune cells or their substitutes, are the direction into which it is worthwhile to delve deeper. These therapies work by using or designing immune cells in a bid to attain usual immune responsiveness and efficacy, for treatment of several illnesses including autoimmune disorders [58,59].

3.3.1 Hematopoietic Stem Cell Transplantation

HSCT is a method for treating severe autoimmune diseases like MS and systemic sclerosis [60]. The process starts with administering high dosing of chemotherapy or immunosuppressive agents which eradicate all the immune cells of the patient [61]. This is succeeded by the transplantation of hematopoietic stem cell that may be harvested from the patient's bone marrow or peripheral blood (autologous) or from a donor who is human leukocyte antigen (HLA) matched (allogeneic) [62]. The general idea is that the new stem cells will replace the immune system and once this new system is in place the body would have no autoimmune disorder causing cells [63]. Trial data indicate that auto-HSCT can produce durable disease remission in disorders such as MS, together with enhanced neurologic function and improved quality of life (QOL). However, the procedure is comparatively risky for patients and can lead to infections as well as problems with organs, so it is most beneficial for patients with severe diseases that do not respond to other types of treatment [36].

3.3.2 CAR T-Cell Therapy

CAR T cell therapy originally was approved for the treatment of hematological cancers but the treatment approach has now been proposed for autoimmune diseases [57]. In this strategy, a patient's T cells are engineered to express CAR that binds to certain antigens on autoreactive B cells or T cells in disease like SLE [64]. For instance, CAR T cells designed to recognize CD19 on the surface of B cells have been used with success in direct ablation of pathological B cells, which are implicated in autoimmune diseases [65]. These initial trials show that CAR T-cell therapy could produce drastic reductions in disease activity and even get rid of the disease in some patients, however, monitoring for potential adverse effects such as cytokine storm has to be done [66].

3.3.3 Treg Therapy

Tregs have since become firmly established as the chief mediators of peripheral immune tolerance, which is essential in inhibiting excessive immune response and autoimmunity [67]. Tregs therapeutic strategies have improved significantly in the last 10 years with emerging phase II-III clinical trials data that continue to support the efficacy and safety of these approaches [68]. Treg therapy is usually applied in cases where autologous $CD4^+CD25^+Foxp3^+$ Tregs of the patient are isolated and expanded under good manufacturing practice conditions, and reintroduced to restore immune homeostasis [69]. Repeatedly, in clinical trials in type 1 diabetes (T1D), adoptive Treg transfer is both safe and capable of sustaining residual pancreatic b-cells, which have been shown in the form of stabilized C-peptide and reduced insulin requirements. Optimization of dosing and repeated infusions have been proposed in more recent phase II studies as potentially improving the durability of these effects without increasing the risk of infection or malignancy. In addition to T1D, Treg-based therapies have also been in phase II trials in other diseases including systemic lupus erythematosus, multiple sclerosis, and IBD in which initial studies have shown an improvement in disease control and a positive tolerability profile [70]. Similar progress has been achieved with tolerogenic vaccines, which stimulate antigen-specific Tregs *in vivo*. Phase II trials with peptide based or dendritic cell based tolerogenic vaccines have demonstrated reductions in disease activity markers with only a small amount of systemic immunosuppression [71]. To enhance Treg stability, persistence, and functional efficacy, combination strategies, involving Treg infusion with low dose IL-2 or tolerogenic vaccines or antigen-specific immunomodulators, are currently undergoing testing in late phase II and early phase III [72]. All these developments highlight the maturity of Treg-based therapies translationally. As refinements in the technology continue and as the tolerant phase III validation is effective, cell-based and tolerance-inducing strategies have a high potential of being capable of offering long-term disease modification-and perhaps long-term remission-to patients with refractory autoimmune diseases [73].

3.4 Gene Editing & RNA based Therapies

Gene-editing and RNA based therapies are novel molecular therapies for immune disorders that target known genetic and molecular deficiencies found in those medical conditions. Most of these therapies afford the means of getting to the roots

of the immune system and may be curative by fixing the faults in the genes and molecular pathways responsible for this abnormality [70-72].

3.4.1 CRISPR-Cas9 for Genetic Correction

Currently, CRISPR-Cas9 can allow for the modification of certain sections of DNA and imagines correcting for some genetic abnormalities behind immune pathology [73]. In monogenic diseases, all that is required for disease development is the mutation of one gene, and CRISPR-Cas9 can be used to fix it. For instance, in X-linked severe combined immunodeficiency (SCID), an immune deficiency disease with potentially lethal outcome caused by a mutated gene in the immune system, previous studies with the help of CRISPR-Cas9 technology to correct the mutated gene [74]. It is also being tested in other genetic immune disorders including Chronic Granulomatous Disease (CGD) in which immune cells have a defect in their ability to mount an effective defense against infection. CRISPR-Cas9 can offer lasting therapeutic impact by restoring normal function in specific immune cells; however,, there is still need to conduct extensive safety experiments, including off-target effects and immune response to the modified cells [75].

3.4.2 RNAi and Antisense Oligonucleotides

RNAi technology also offers a further approach to immunosuppressive techniques-inactivation of genes that are responsible for inflammation reactions. short interfering RNAs (siRNAs) in RNAi are functional to bind and degrade target mRNA sequences so that the proteins, which entail disease, are not synthesized [76]. In immune disorders, then, RNAi can be applied to prevent or reduce the production of activators including TNF-α or IL-6, which is an activator in RA or Crohn's disease, respectively. For example, IRAK4 mRNA which is aimed at selective decrease of inflammation at molecular level is being developed for autoimmune disorders using RNA based drug RNAi [77]. There are other RNA-based strategies which are differing in the way they interact with the target mRNAs – antisense oligonucleotides (ASOs) that binds to the particular subsequences of mRNA thus preventing further translation of the mRNA into protein [78]. ASOs work well in conditions such autoimmune related disorders such as IBD and lupus where one can manipulate inflammation to with positive results [79,80]. In comparison, to small molecule drugs and biologics, ASOs and rian RNAi therapies are highly specific in their activity, mean and may result in fewer side effects [81]. The current treatment of immune disorders has been boosted by gene-editing and RNA-based therapies since they target disease pathways accurately. Although in early concept definition phase for many they represent a conceptual shift toward 'cures' for genetic immune disorders and conditions that are mediated by identifiable and targetable molecular pathways. Further study is required for refining safety, delivery and efficiency for more extensive utilization in clinical practices [82].

3.5 Precision Medicine in Autoimmune Diseases

Major advancement in the management of immune disorders is the concept of personalized medicine which addresses individual genetic, biomarker and immunological differences to prescribe specific treatments for the patient. This strategy increases the effectiveness of the treatment without having to pay the price for the side effects, thus improving patient satisfaction [83,84].

3.5.1 Biomarker-Guided Therapy

Biomarkers help in guiding the prognostic frameworks and one of the most important issues in the development of precision medicine is the use of biomarkers that define immunological processes. For instance, the values of given cytokines are indicative of the ways the given patient may react to particular therapies [85]. In psoriasis, patients with high IL-17A have better outcomes with anti-IL-17 treatment like secukinumab, and that high levels of both cytokines are present in psoriatic arthritis patients. With the help of these biomarkers, clinicians will be able to choose the proper therapy for a particular patient, usually avoiding the attempts that prove to be ineffective due to individual differences in the results [86].

3.5.2 Pharmacogenomics

Pharmacogenomics is concerned with the study of how genetic differences affect people's attitudes towards medicines. This field is more applicable in cases of autoimmune diseases where people's genes determine how they will respond to compound in a drug [87]. For instance, genetic differences in drug-metabolizing enzymes or receptors whose genes are involved in the metabolism and action of these drugs can impact the effectiveness of interventions such as JAK inhibitors. By incorporating pharmacogenomic data into clinical care, health care professionals can develop the best treatment regimens for patients galore enormously from his/her genetic profile [88]. The concept of immunopharmacotherapy and personalised and precision medicine is aimed at changing the approach to immune disorders where treatment plans will be developed based on the persons immune system. This way not only the results of the treatment becomes better but also the satisfaction of the patient when therapies are chosen in accordance with his or her abnormalities and peculiarities will be increased. In the ongoing progress of new knowledge, the practical application of the personalized approach is promising for the future of immune disorder treatment [89].

4. Issues and Prospect

Although the development of immune therapeutics has improved remarkably within the last decade, several issues still occur that limit the extent to which patients can benefit and the extent to which they can be integrated. Figure 2 summarized challenges associated with some novel therapeutics used in management of immune disorders such as safety concerns, long term efficacy, cost and availability.

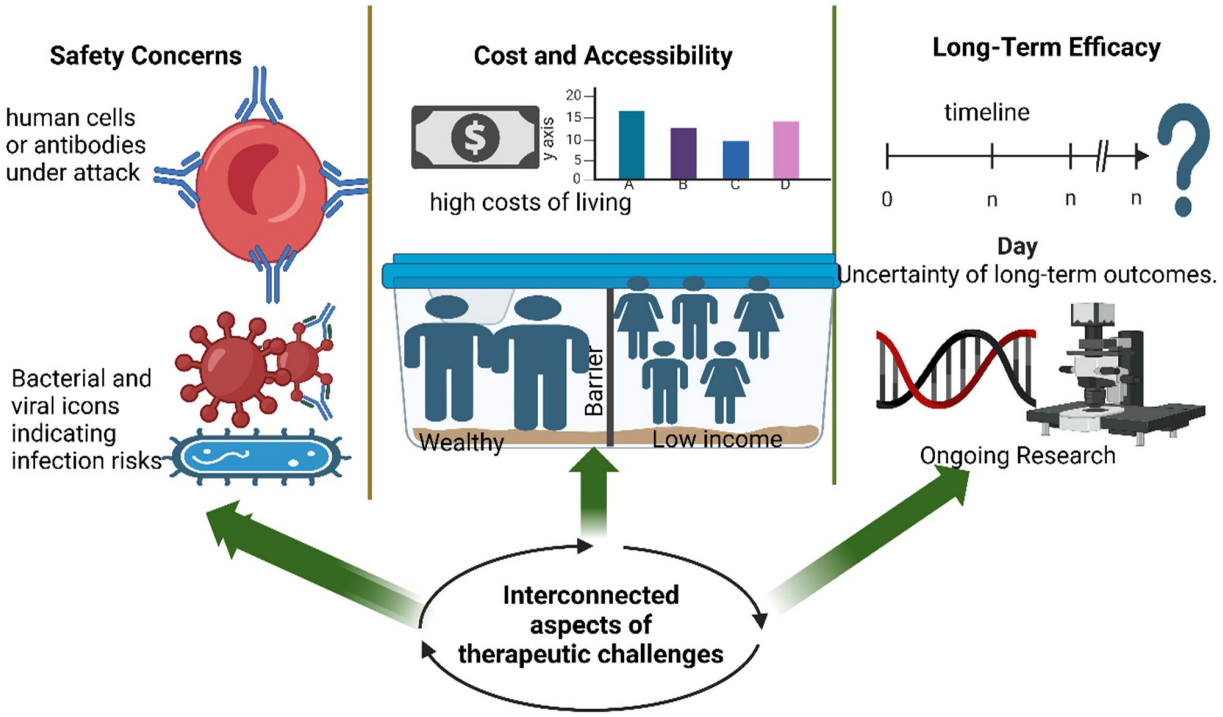


Figure 2. Common concerns associated with available immunological therapeutics.

4.1 Safety Concerns

A large number of new agents, including many biologic and JAK inhibitors, have immunosuppressive effects and increase the risk of infection and malignancy. First of all, patients under anti-TNF treatment may be at increased risk for developing complications of previously unrecognized infections, such as reactivation of latent tuberculosis [90].

4.2 Cost and Accessibility

The development costs incurred in biologics, gene therapies, as well as cell-based therapies present a huge challenge with regard to affordability most substantially in LMICs. Due to the high cost of caring for metastatic patients, alone or in combination with other treatments, these innovative therapies may be available only to the higher strata of society and reduce socio-economic differences in the effectiveness of treatments [91].

4.3 Long-Term Efficacy

While hopeful, long term outcomes and remission durability of responses to other classes of therapies, which include gene therapies and CAR T cell therapies, are not yet established. Another area if interest for research is the mid and long-term outcomes of this therapies in order to evaluate the safety and efficacy of his treatments. This is particularly so for therapies that manipulate the immune system since there are likely to be other side effects that are unpredictable [92].

5. Future Directions

5.1 Technical Pathways: Emerging Platforms and Synergies

The future of immunological disorders treatment is geared towards precision, safety and synergy. A new generation of immunomodulatory platforms with reduced systemic toxicity and greater therapeutic specificity is the new direction that drug developers are taking. Biologic innovations, including monoclonal antibodies, cytokine inhibitors, engineered cell therapies, etc., are being optimized to have strong immunoregulatory properties, with fewer safety issues than existing conventional therapies. How to deliver therapeutic action to particular immune compartments and limit systemic dissemination and off-target effects of therapeutic agents is a promising research direction today [93-95] The combination of biologics with small-molecule therapeutics or targeted immunosuppressants is also an exciting future research direction.

These regimens prove to be particularly effective with patients that are not responsive to the monotherapies. With these kinds of synergies, drug doses can be reduced and this means fewer cases of adverse reactions and more effectiveness. One of the rapidly advancing frontiers is immunotherapies against immune tolerance, such as high-dose Tregs infusions engineered to express Tregs. These Tregs are made to re-tune immune responses hence room pathological autoimmunity with minimal general immune impairment. Also, tolerogenic vaccines are being studied and examined due to their ability to re-train the immune response to tolerate self-antigens and not result in immune reactions which provide a proactive form of disease prevention and long-term remission [96,97].

5.2 Translational Dilemmas: Scalability and Equity

Although these are made, there are major challenges in translation. Scalability is one of the key obstacles since many novel immunotherapies like Treg therapies or tolerogenic vaccines are difficult to manufacture and demand substantial infrastructure, which is only affordable in resource-rich environments [98]. The large scale use of clinical settings requires the use of strong scaling models that are able to support health disparities across the world. Another constraint that is very crucial is cost. The process of high development and production costs of biologics and personalized immune therapies produces high financial cost burden on the patients, especially in low- and middle-income countries. The realization of equity in the access will involve strategic alliances, policy changes, and adaptive pricing to make certain life-saving innovations are not instruments of exclusion. Moreover, these new therapies are still undergoing development in long-term safety profiles and regulations. Issues on longevity of immune tolerance, immunosuppression risks, and possible oncolytic nature have to be resolved by thorough longitudinal research and standard clinical practices. The field can only see the promise of next-generation immune disorder therapeutics achieved by developing technical innovation and tackling the issue of translational bottlenecks simultaneously.

Consent to Publish

All authors consented to the publication of this article.

Data Availability Statement

Data sharing is not applicable as no datasets were generated being a review article.

Competing Interest

Authors declare no competing interests to the best of their knowledge.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Abbreviations

CRISPR: Clustered regularly interspaced short palindromic repeats

CAR T cell: Chimeric antigen receptor T-cell

HSCT: Hematopoietic stem cell transplantation

IL: Interleukin

IBD: Inflammatory bowel disease

JAK: Janus kinase

PDE-4: Phosphodiesterase-4

RA: Rheumatoid arthritis

RCTs: Randomized controlled trials

RNA: Ribonucleic acid

S1P: Sphingosine-1-phosphate

TNF: Tumour necrosis factor

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